

## REMARKS

Applicants respectfully request reconsideration of the present application in view of the following commentary.

### **I. Introduction**

As the Examiner indicates that the Amendment and Response filed on April 7, 2008 has been entered, claims 1-10, 13-17 and 56-57 are under examination, with claims 11-12 and 18-55 withdrawn. No further claim amendments are made in this response.

### **II. Rejection of Claims under 35 U.S.C. § 103(a)**

#### **A. Ramirez**

Claims 1-10 and 56-57 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over U.S. Patent No. 5,632,996 to Ramirez *et al.* (“Ramirez”). Applicants respectfully traverse the rejection.

Benzoyl peroxide is known in the art to be “sparingly soluble in water and alcohol and soluble in benzene, chloroform, and ether” (specification, page 5, lines 8-9). Therefore, the formulation of benzoyl peroxide, represented by that of Ramirez, “requires solubilization of the benzoyl peroxide,” and “[t]he solubilizing agent can be an irritant, and may contribute to adverse reactions to the dosage form” (specification, page 7, lines 10-12). More specifically, Ramirez describes a formulation, in which benzoyl peroxide is solubilized in alkylbenzoate.

In contrast, the claimed invention relates to a nanoparticulate benzoyl peroxide composition that does not require the presence of any solvent. As one skilled in the art would have understood, “dissolving” poorly water soluble drugs, such as benzoyl peroxide, in water is extremely difficult. To be absorbed and have a pharmaceutical effect, a drug must be dissolved first, if not in water, at least in an organic solvent. However, many organic solvents have adverse

side effects to animals and humans. The invention addresses the solubility problem by decreasing the particle size of the drug to increase the bioavailability of the drug, such that the formulation can even be used in a liquid wash without the presence of organic solvents. *See* specification, page 9, lines 4-6 and 8-9. In contrast to the claimed composition, Ramirez's composition requires the presence of alkylbenzoate. Accordingly, the claimed nanoparticulate benzoyl peroxide composition, which is stabilized by a surface stabilizer to maintain the effective average particle size of the benzoyl peroxide particles, is distinguished from the benzoyl peroxide composition of Ramirez, which is dissolved in a solvent, alkylbenzoate.

The Examiner contends that the advantages of the claimed nanoparticulate benzoyl peroxide composition is not convincing because there is no comparison to the benzoyl peroxide compositions of the prior art (Advisory Action, page 2, second paragraph, last three lines). Applicants respectfully direct the Examiner's attention to the specification, page 14, paragraph [0050]. In the disclosure, the claimed benzoyl peroxide nanoparticulate composition is compared to the conventional benzoyl peroxide composition and the claimed composition shows superior viscosity, less than about 1/25 to less than about 1/200 of a conventional formulation, at about the same concentration per ml of benzoyl peroxide.

Turning to the references by Tarasov, Self and Bagchi, the Examiner asserts that Applicants "directly ignore" that: (i) Bagchi teaches small particles of less than 400 nm; (ii) Bagchi requires that surface active agents must be added to successfully precipitate particles of such small size; (iii) surface active agents cited by the Examiner in Bagchi are in some instances the same as those claimed by Applicants; and (iv) the similarities of Tarasov and Bagchi provide evidence that one of ordinary skill in the art would be able to make and optimize the size of benzoyl peroxide particles before the claimed invention was made.

In the prior response, Applicants did not ignore any evidence in the prior art. Rather, Applicants pointed out that none of these secondary references specifically relate to nanoparticulate benzoyl peroxide compositions. For instance, Bagchi relates to pharmaceutical

agents having a particle size of less than 400 nm but does not disclose benzoyl peroxide as one of the pharmaceutical agents. Tarasov relates to benzyol peroxide, but the particle size of benzyol peroxide is from about 0.25 mm (corresponds to 250,000 nm) to about 10 microns. Self disclose a benzyol peroxide dispersion having a particle size of less than 10 microns, preferably from about 2 to about 5 microns. As such, there is no evidence on the record showing that nanoparticulate benzoyl peroxide composition can be successfully obtained at the time of the invention, particularly in view of the teaching of U.S. Patent No. 5,14,684 that not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition.

The Examiner dismissed Applicants' arguments based on KSR by stating that "since the particles of the invention and the particles disclosed by the prior art are substantially similar and any modification would have been within the ordinary skill of the artisan in this art" (Advisory Action, page 3, first paragraph). Applicants respectfully disagree.

Although the benzoyl peroxide particles *per se* of the invention and the prior art are essentially same, they are different in size, which results in different formulations with different properties. One skilled in the art may have been motivated to reduce the particle size of benzoyl peroxide, the Examiner has not provided any evidence to show that there is reasonable expectation of success, in view of the prior-art teaching that not every combination of surface stabilizer and active agent will result in stable nanoparticulate compositions.

Accordingly, Applicants respectfully request withdrawal of the rejection over Ramirez.

**B. Ramirez and Kanios**

Claims 1-10, 14-16 and 56-57 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Ramirez in view of U.S. Patent No. 5,719,197 to Kanios et al. ("Kanios"). Applicants respectfully traverse the rejection.

Ramirez is discussed *supra*. Kanios is cited for allegedly teaching bioadhesive carriers and additional active agents. However, Kanios does not remedy the deficiencies of the primary references by teaching a nanoparticulate composition of benzoyl peroxide having an effective particle size of less than 2000 nm, and a surface stabilizer associated with the surface thereof. Accordingly, the obviousness rejection should be withdrawn.

**C. Ramirez, Kanios, and Bartnick**

Claims 1-10, 13-17 and 56-57 are rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Ramirez in view of Kanios and U.S. Patent No. 5,399,35 to Bartnick et al. ("Bartnick"). Applicants respectfully traverse the rejection.

Ramirez and Kanios are discussed *supra*. Bartnick is cited for allegedly teaching the inclusion of antibiotics, lactic acid, PVP, lysozyme, etc. in a composition to disinfect undamaged skin. Bartnick is not even related to a nanoparticulate composition of benzoyl peroxide, and does not provide any teaching of benzoyl peroxide particles having an effective particle size of less than 2000 nm, or a surface stabilizer associated with the surface thereof. Thus, the combined teachings of all of the cited references fail to render the claimed invention obvious. Accordingly, Applicants respectfully request withdrawal of the obviousness rejection.

**CONCLUSION**

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the

undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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